NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2005

PLAN FOR HIV-RELATED RESEARCH

I: NATURAL HISTORY AND EPIDEMIOLOGY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

The features of the HIV/AIDS epidemic in the industrialized and the developing world are under continuous scrutiny and re-evaluation by the scientific community with the ultimate goal of developing effective means of prevention and treatment. In the United States and other industrialized countries, the second half of the 1990s witnessed steep declines in deaths and AIDS diagnoses among HIV-infected individuals. Such improvements, attributable to the widespread use of new and effective treatment regimens, have markedly slowed down in the last several years. While changes in the treatment backdrop influence the type and scope of new scientific investigations, other factors continue to change the composition of the epidemic in the United States and elsewhere. New HIV infections occur more frequently in racial and ethnic minorities, groups with high-risk sexual behaviors, injecting drug users, and adolescents. The use of potent antiretroviral therapy (ART) has extended the time between HIV infection and development of AIDS, resulting in people living long enough to develop age-related co-morbidities that previously were rarely observed.

The spread of the HIV epidemic in resource-poor countries, while continuing unabated in most places, is characterized by its heterogeneity, with heterosexual transmission and drug use being the factors most consistently found to fuel the epidemic. NIH-sponsored studies on HIV/AIDS in developing countries have increased in number and scope. Well-designed epidemiological investigations are particularly needed to characterize the local epidemics and disentangle the respective effects of viral, host, and

environmental factors on HIV transmission and disease progression. These investigations will serve as the basis for designing rational, evidence-based interventions. As more and more treatment modalities are tested in the developing world, close monitoring of desired and undesired effects (e.g., toxicities, viral resistance) of such treatment approaches will also be necessary.

PRIORITY FOR FUTURE RESEARCH:

- **Sponsor domestic and international epidemiologic studies to characterize modes of transmission, including host characteristics (e.g., sexual behavior, substance use, use of blood products and other injections, genetic variations) and viral characteristics (e.g., subtype, resistance, tropism), or continued risk behaviors in HIV-infected and uninfected populations of adults, adolescents, and children.**

Studies of certain HIV transmission modalities, such as mother-to-child transmission (MTCT), have resulted in the successful testing of prevention measures and continue to produce applicable methods of decreasing HIV transmission rates in the developing world to the low levels achieved in the industrialized world. Other transmission avenues, however, are still less well known in their biological and behavioral determinants. These include instances of heterosexual transmission in which the interplay of host and viral characteristics may result in variable degrees of transmission probability. In a setting of rapid and continued evolution of the virus, the monitoring of such viral features as recombination and development of resistance to antiretrovirals (ARVs) is critically important to curtail transmission. Rigorous NIH-sponsored epidemiological studies are needed for the detailed characterization of risk factors for HIV transmission in different populations, including increases in risk behaviors by individuals who receive interventions. The ability to design effective interventions that curtail transmission of HIV rests on further research of determinants and co-factors of HIV transmission.

PRIORITY FOR FUTURE RESEARCH:

- **Implement epidemiologic studies (including those of host genetics and other modifiers of host response, viral genetics, and transmission characteristics) to monitor, inform, and evaluate intervention strategies and surveillance in domestic and international settings.**

As the HIV/AIDS epidemic spreads in new locales around the world, population-based studies are of critical importance to describe the rate of epidemic expansion and the factors that may accelerate or slow its progress. The knowledge of such factors, gained through NIH-funded

research, will inform the design of intervention strategies that are evidence-based, generalizable, sustainable over the long term, and—in the case of resource-poor countries—affordable in the face of competing health needs. There will need to be a quantitative assessment of the impact of interventions on risk-taking behavior, particularly as standardized interventions are applied to widely different circumstances. Furthermore, as more intervention approaches are developed and implemented, epidemiologic studies will have to incorporate cost-effectiveness outcomes and analyses. This is of particular importance for developing countries where resources are limited.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of recent infection for high-throughput use in domestic and international settings.**

The availability of accurate and reproducible laboratory assays is a critical factor to rapidly acquire knowledge of the HIV epidemic in different populations and geographic areas. Assays are needed to screen populations for HIV-related or host-related factors that may affect the diagnosis, prognosis, and treatment of HIV/AIDS. In developing countries, simple, fast, and affordable assays are necessary to define the epidemiologic features of emerging or evolving epidemics and for clinical use in hard-to-reach areas. There is a particular need to develop and evaluate assays that are self-contained and have long shelf life under unfavorable environmental conditions.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics to establish databases that support analyses of host and viral characteristics. Use this approach to increase the understanding of the pathogenesis of HIV infection and disease, including adverse events in the presence of interventions.**

The development and maintenance of a domestic and international infrastructure is necessary for the study of biological and behavioral aspects of HIV/AIDS in new or previously understudied populations. The NIH will continue to emphasize the importance of cohort studies to investigate the rate of disease progression, the causes of death, and the impact of therapy on the changing spectrum of HIV disease. In addition, such studies will provide an opportunity to start new pathogenetic investigations using biological specimens collected in controlled

circumstances and from highly characterized study participants. The availability of specimen repositories from long-term studies will allow the exploration of toxic effects of drugs and of the variable occurrence of adverse events in genetically varied populations. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key co-factors (e.g., infectious, nutritional, host genetic-related) that modify HIV disease and might affect its response to treatment or vaccines. Enabling technologies, including bio-informatics, will be key NIH instruments in increasing the quality of NIH-supported research and the widespread dissemination of its findings.

PRIORITY FOR FUTURE RESEARCH:

- **Characterize the interactions between HIV, host genetics, and the major environmental factors that influence outcomes (viral transmission, response to therapy, and disease progression). This includes how variants of viral genes (e.g., those accounting for subtypes and drug resistance) interact with the host in the context of different routes of transmission, co-morbidities, and host genetic variants or other determinants of the immune response.**

The science of the interaction between host and nonhost (viral, environmental) components is an exceedingly complex one and includes the exploration of many diverse factors that might determine or influence specific outcomes. The role of host genetic variation on HIV transmission and control needs to be further explored, especially in domestic and international populations that have different racial and ethnic make-up. The NIH will support studies investigating the pattern of involvement of host genetic polymorphisms and their effects on HIV transmission and disease progression. Studies are needed to determine the effect of concomitant infections on immunogenicity and efficacy of HIV vaccine candidates. Similarly, studies may also allow for the identification of natural determinants of ARV resistance that might compound resistance driven by drug exposure. A broader assessment of the effect of the environment is also warranted, including physical and social factors that might affect HIV-related outcomes.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention strategies.

STRATEGIES:

- Identify, establish, and maintain cohorts in which HIV transmission and acquisition can be assessed, including incident cohorts.
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, antiretroviral resistance mutants, multiple subtypes, and recombinant virus.
- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral quantity (measures of viral RNA and other quantification methods) in various body compartments (e.g., blood, saliva, and mucosal compartments) and HIV genotype, including subtypes, recombinants, resistance mutants, and dual virus infections;
  - Host factors such as age, sex, hormonal status, strength and breadth of immune response, mental health, history of alcohol and drug use, and host genetic factors;
  - Modifiable host factors such as nutritional status; drug, alcohol, and tobacco use; use of exogenous hormones; other infections, including oral infections; other causes of mucosal pathology, including sexually transmitted diseases (STDs); and circadian rhythm;
  - Use of microbicides and barrier devices;
  - Social, cultural, behavioral, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, gender, culture, community, and geographic location (e.g., rural, urban, suburban);
  - Sexual activity, choice of partner, duration of partnership, control of STDs, hygienic practices, contraception choices, and cultural practices such as use of traditional vaginal preparations, female genital mutilation, and male circumcision;
  - Health care issues, including access, quality, sustainability, and education for prevention; and

  - Extent to which environmental and other macro-level factors such as war, migration, drug trafficking patterns, political will, and disasters influence vulnerability, risk behaviors, acquisition, and access to care in developed and developing countries.

- Conduct epidemiological studies to assess whether the prevalence or incidence of hepatitis C (HCV) may serve as a predictor of HIV epidemics in world areas faced with a potentially explosive epidemic of HIV.

- Evaluate the impact on HIV transmission of hormonal contraceptives and replacement therapies, hormonal composition of such therapies, pharmacokinetics, and duration of action of repository form contraceptives.

- Evaluate the impact on HIV transmission of antiretroviral therapies, medication adherence, and related factors such as therapy and regimen characteristics, HIV incidence, drug effectiveness, symptom management, and impact of viral load suppression on patterns of risk behavior.

- Employ epidemiological techniques to evaluate and quantify the impact of different intervention strategies on HIV transmission and prevention.

- Evaluate risks, benefits, and cost-effectiveness of providing prophylaxis against HIV infection after occupational and parenteral exposures to HIV.

- Examine the effects of vaccine trials on HIV transmission characteristics, including the effects on the alteration of transmission by vaccine-induced immunity. Examine the clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on viral load, rates of progression, and on population HIV incidence.

- Conduct studies on medication-assisted substance abuse treatment modalities (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, antabuse, acamprosate, and stimulant abuse therapy) alone or in combination with behavioral interventions as HIV prevention interventions.

- Identify effective individual, network, and community-level interventions and determine the coverage needed to prevent, arrest, and reverse HIV epidemics in developing and developed countries.

- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance.
  - Establish optimal antiretroviral regimens for pregnant women.
  - Assess the impact of breastfeeding practices on MTCT of HIV and on the health of children and mothers.
  - Define how the physiology of lactation impacts on HIV transmission.
  - Assess the impact of maternal antiretroviral regimens of different potency and duration on MTCT of HIV and on the health of women eligible for antiretroviral therapy.
  - Study the safety and effectiveness of low-cost, sustainable approaches to prevention of MTCT of HIV, including exclusive breastfeeding in the first months of life with rapid weaning.
  - Determine the long-term effects of measures to prevent perinatal infection.
  - Assess the impact of postnatal antiretroviral prophylaxis of children on MTCT of HIV.
  - Assess the impact of perinatal treatment and prophylaxis regimens on community-wide HIV resistance to antiretrovirals.
- Conduct studies that concurrently address HIV and HCV by incorporating research on HCV infection within existing programs of research on HIV/AIDS (e.g., MTCT).

OBJECTIVE - B:

Use epidemiological research in domestic and international settings to identify the influence of therapeutic and other biological (e.g., co-infections) and behavioral (e.g., access) factors on HIV progression, as shown by virologic, immunologic, and clinical outcomes.

STRATEGIES:

- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects (including host genetic factors and their modulators, sex, race, and age).
- Evaluate the effects of modifiable host characteristics on viral measures, immune function, disease progression, and mechanisms for these effects.
- Investigate the effect on disease progression of viral factors, including viral genotype, phenotype, and acquired drug resistance to antiretroviral drugs.
- Evaluate the impact of treatment of alcohol abuse, drug abuse, and mental health disorders on the effectiveness of antiretroviral therapy.
- Identify the individual, provider, and structural factors associated with initiating, continuing, and discontinuing antiretroviral therapy.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies.
- Determine the global patterns of viral resistance (innate and acquired) to antiretroviral therapies and how these patterns could influence the long-term effectiveness of these therapies.
- Evaluate the rate of HIV disease progression in conjunction with the effects of feasible interventions (antiretroviral and other prophylactic) in international settings and in populations with different HIV subtypes and variable co-factors such as nutrition and opportunistic infections (OIs).
- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease and evaluate interventions, including indigenous approaches, especially in minority populations and developing countries. Emphasis should be placed on cohorts that allow for subgroup comparisons.

- Continue to characterize the epidemiology of HIV/AIDS infection among those who have minimal exposure to antiretroviral therapies, those who have virologic and/or immunologic responses to these therapies, and those who have failed these therapies.
- Evaluate the long-term complications of antiretroviral therapy on exposed, HIV-uninfected children.
- Examine the effect of the health status of HIV-infected mothers on survival of their children, both HIV-infected and uninfected.
- Identify the effects of long-term exposure to HIV therapies on other infectious diseases; malignancies and associated oncogenic infections; cardiovascular disease; and other HIV-associated diseases, including central and peripheral nervous system conditions, oral and mucosal lesions, wasting and other metabolic disorders, and renal, hepatic, bone, and endocrine complications.
- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined population subgroups, including the factors that influence residual HIV replication in antiretroviral treatment recipients.
- Investigate how different patterns of access, adherence, and exposure to drug regimens in treatment-experienced and treatment-inexperienced populations contribute to HIV drug resistance and disease progression.
- Assess the effect of HIV on other infections (e.g., GB virus C [GBV-C or hepatitis G], hepatitis C [HCV], hepatitis B [HBV], human papillomaviruses, other blood-borne infections, tuberculosis, and malaria and other parasitic diseases) and the effect of these infections and their treatment on HIV outcomes.
- Encourage natural history studies that address both HIV and HCV infections and incorporate research on HCV infection within existing programs of research on HIV/AIDS.
- Study HIV-infected children and adolescents to determine factors related to impaired growth and neurodevelopment, impact of other childhood infectious diseases, safety and efficacy of immunizations, and how these may be affected by medical and behavioral interventions.
- Study the effect of HIV infection and its treatment in aging populations with coexisting morbidities and polypharmacy.

- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., multidrug-resistant tuberculosis, sulfa-resistant malaria, cotrimoxazole-resistant *Pneumocystis carinii* pneumonia [PCP], and lamivudine-resistant HBV) in HIV-infected populations.
- Study determinants of adherence to antiretroviral therapy, including the role of traditional approaches, and adverse events of such therapies in international settings.

OBJECTIVE - C:

Develop and evaluate methods and resources for epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods and information systems; and better integrate research findings into clinical practice and regional, national, and international policy.

STRATEGIES:

- Evaluate and promote the use of study designs that incorporate appropriate ethical, cultural, and policy context for studies in diverse domestic and international populations.
- Support training and mentorship of medical and health professionals in developing countries in the areas of research ethics, study design, data management and analysis, and linking clinical care to health policy.

Strategies Related to Natural History/Pathogenesis

- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on staging disease progression for the initiation and monitoring of HIV therapy and OI prophylaxis, HIV resistance testing, and noninvasive diagnostic assays for STDs, other OIs including tuberculosis, and AIDS-related malignancies.
- Develop, evaluate, and validate diagnostic assays for rapid HIV detection for both chronic and primary HIV infection, including detuned assays and assays useful in conjunction with interventions to reduce MTCT.
- Develop new epidemiological designs and statistical methods to better characterize transmission dynamics and monitor long-term trends in disease progression in the setting of potent ART.
- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these resources should be particularly encouraged and developed.
- Support cross-cohort studies to explain the variability in the natural history of HCV infection and HIV co-infection rates in individuals infected with different HCV genotypes (e.g., in China) and the implications of this variability for development of vaccines and treatments.

- Use observational data to better characterize the natural history of OIs in international settings and trends in the epidemiology of these conditions.
- Develop methods for assessing HIV-related quality of life that are feasible and culturally appropriate.

Strategies Related to Interventions

- Study the various operational strategies that can be employed to "bring to scale" ART programs.
- Assess the effectiveness and comparability of clinical versus laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-poor settings.
- Develop appropriate clinical and laboratory definitions of short-term and long-term antiretroviral failure.
- Evaluate the impact of continued antiretroviral therapy after the failure of multiple regimens.
- For prevention studies in both domestic and international settings, improve approaches for recruitment and retention of populations now underrepresented in such studies, including minorities, children, adolescents, women, drug and alcohol abusers, incarcerated populations, and persons living with mental illness.
- Study the impact of access to ART and vaccines on risk behaviors and HIV acquisition among at-risk populations.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, medical treatments, and other iatrogenic exposures in developing countries, including instrument sterilization.
- Assess the impact of different strategies for HIV testing and their linkage to care.

Strategies Related to Policy

- Evaluate the long-term clinical impact of different strategies for care, including OI prophylaxis and ART.
- Assess the impact and cost-effectiveness of different aspects of HIV clinical care from an individual and societal perspective.

- Develop methods for disseminating research and linking research results to regional and national standards of care, including formal HIV practice guidelines.
- Develop formal methods to assess the applicability and transportability of guidelines for care across countries.
- Support HIV policy research, including economic impact studies, necessary for translating epidemiological and clinical studies into policy.
- Identify the effects on HIV transmission and treatment access of changes in drug enforcement policies and activities in domestic and international settings.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities

APPENDIX B:

FY 2005 OAR Planning Group for Natural History and Epidemiology

FY 2005 NATURAL HISTORY AND EPIDEMIOLOGY PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	*Pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

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